Niche-Focused Research: Discovery & Development of Hematopoietic Regenerative Factors

Grant Award Details

Niche-Focused Research: Discovery & Development of Hematopoietic Regenerative Factors

Grant Type: Research Leadership

Grant Number: LA1-08014

Project Objective: The goals of the research program are to 1) use murine genetic models to identify niche factors that promote growth and self-renewal of hematopoietic stem cells (HSCs); and 2) use the newly discovered niche factors to develop pharmacologic therapies for accelerating HSC regeneration in myelosuppressed or myeloablated patients

Investigator:

Name:	John Chute
Institution:	University of California, Los Angeles
Type:	PI

Disease Focus: Blood Disorders

Human Stem Cell Use: Adult Stem Cell

Award Value: $5,174,715

Status: Active

Progress Reports

Reporting Period: Year 1

View Report

Reporting Period: Year 2

View Report

Grant Application Details

Application Title: Niche-Focused Research: Discovery & Development of Hematopoietic Regenerative Factors

Public Abstract: Bone marrow and peripheral blood transplantation utilizing blood stem cells can provide curative treatment for patients with cancers and non-cancerous diseases of the blood and immune systems. Such treatments can be curative because the stem cells contained within the bone marrow or peripheral blood of healthy donors are capable of replacing the entirety of the patient's blood system and providing a new immune system which can eradicate the patient's cancer cells. The application of blood stem cell transplantation could be applied to a much larger population of patients if methods could be developed to expand blood stem cells in vitro or in vivo. This would be particularly beneficial for the broadened application of human cord blood transplantation for the many patients who lack an immune-matched sibling or unrelated donor. Furthermore, a method to expand human blood stem cells in vivo could be highly beneficial for the thousands of patients with cancer who require toxic chemotherapy which frequently results in decreased blood counts, infections and bleeding complications. A systemic treatment (i.e. a shot) which could cause blood stem cells to grow and produce more blood cells in patients could markedly improve patient's outcomes after they receive such chemotherapy in the curative treatment of cancer. However, the development of treatments capable of inducing human blood stem cells to grow in the body has been very slow, in part due to a lack of understanding of the processes which govern blood stem cell growth in general. In my laboratory, we have developed mouse genetic models which allow us to discover new proteins produced in the bone marrow (the "soil" where blood stem cells reside) which make blood stem cells grow. We have recently discovered that 2 proteins are secreted by blood vessels within the bone marrow and cause blood stem cells to grow rapidly following damage with radiation. We are currently in the process of developing one of these into a growth factor that we can deliver to patients via injection as a means to cause their blood stem cells to grow after cord blood transplantation or following chemotherapy treatment for cancer. In this proposal, we will utilize our unique mouse models to discover the additional growth factors that make blood stem cells grow and we will perform pre-clinical studies to test whether these newly discovered growth factors can cause human blood stem cells to grow in vitro and in vivo. This proposal has the potential to generate new understanding of how human stem cells grow in vivo and to facilitate the development of new therapies which can regenerate human blood stem cells and the blood system as a whole in patients.

Statement of Benefit to California:	My research program has both basic science and pre-clinical components which I believe will benefit California in several important ways: First, my basic research program will contribute new fundamental knowledge in stem cell biology which will benefit students, fellows and faculty. My research will also synergize with other campus laboratories and other centers in California and will lead to collaborations and accelerated translation of these discoveries for regenerative medicine. Second, my research program has the potential to directly benefit patients in California. We have already discovered two niche-derived proteins which promote hematopoietic stem cell regeneration in vivo and are focusing substantial efforts now to develop these proteins as therapeutics for Phase I clinical trials. For example, we are developing one of the HSC regenerative factors which we discovered for a Phase I clinical trial to test its efficacy as a systemic therapy to accelerate cord blood engraftment and hematologic recovery in adult cord blood transplant patients. This has literal potential benefit for patients since approximately 10% of cord blood transplant patients die from complications of graft failure or delayed hematologic recovery. In addition, patients with cancer who receive myelosuppressive chemotherapy can potentially benefit from systemic administration of [REDACTED] or other HSC regenerative factors that we discover to accelerate hematologic recovery after chemotherapy. If we are able to show that administration of such regenerative factors can accelerate hematologic recovery in patients after chemotherapy, then remission rates for cancer patients may increase via more effective delivery of curative chemotherapy on time and to completion. Third, my research will provide new intellectual property. These inventions from my laboratory will be available for licensure to biotech or pharmaceutical companies in California. I have experience with licensing inventions from my laboratory to biotech companies and am eager to see my future inventions licensed to accelerate development for regenerative medicine. Fourth, my research program will provide new jobs and professional opportunities. At present, my research program provides partial or complete funding for more than 30 employees internally and more than 30 employees at our partner institutions in academia and biotechnology. I will also bring substantial federal research funding with me to California and will be hiring new fellows, technicians and faculty promptly upon my arrival. Taken together, I am hopeful that my research program will have a major benefit for the scientific community of California, for patients who may benefit from treatments we are developing, for the biotechnology community via the development of new intellectual property and for the larger economy via the creation of many new jobs. I sincerely look forward to the opportunity to bring my program to California.